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Jejunal control of glucose homeostasis in the human body

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Tallen, Barnkliniken, Östra Sjukhuset, Göteborg den 9 december 2021, klockan 13.00 av

Erik Elebring

Fakultetsopponent:
Professor Jan Eriksson
Uppsala universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Wallenius V, Elias E, **Elebring E**, Haisma B, Casselbrant A, Larraufie P, Spak E, Reimann F, le Roux CW, Docherty NG, Gribble FM, Fändriks L. Suppression of enteroendocrine cell glucagon-like peptide (GLP)-1 release by fat-induced small intestinal ketogenesis: a mechanism targeted by Roux-en-Y gastric bypass surgery but not by preoperative very-low-calorie diet. Gut 2020; 69(8): 1423-1431.

II. Wallenius V[#], **Elebring E**[#], Casselbrant A[#], Laurenius A, le Roux CW, Docherty NG, Biörserud C, Björnfot N, Engström M, Marschall HU, Fändriks L. [#] Shared first authorship. Glycemic control and metabolic adaptation in response to high-fat versus high-carbohydrate diets – data from a randomized cross-over study in healthy subjects. Nutrients 2021; 13(10): 3322.

III. **Elebring E**[#], Wallenius V[#], Casselbrant A[#], Docherty NG, le Roux CW, Marschall HU, Fändriks L. [#] Shared first authorship. A fatty diet induces a jejunal ketogenesis which inhibits local SGLT1-based glucose transport – results from a randomized cross-over study between iso-caloric high-fat versus high-carbohydrate diets in healthy volunteers. Manuscript.

IV. **Elebring E**, Casselbrant A, Fändriks L, Wallenius V. The ketone body β-hydroxybutyrate inhibits glucagon-like peptide-1 (GLP-1) secretion through a G-protein coupled receptor mediated mechanism in GLUTag and human enteroid cells. Manuscript.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Jejunal control of glucose homeostasis in the human body

Erik Elebring

Department of Surgery, Institute of Clinical Sciences,
Sahlgrenska Academy, University of Gothenburg, Sweden.

Abstract

Background: The prevalence of obesity and type-2 diabetes mellitus (T2DM) have risen dramatically over the last decades. Recent findings demonstrate that the improved glucose homeostasis following Roux-en-Y gastric bypass (RYGB) is partially weight-loss independent and seen already before the patients leave the operating hospital. Therefore, it has been speculated that this improvement is induced by the reconfiguration of the gut. The exact mechanism for this has been elusive. The overall aim was to investigate how jejunum, and the expression of different proteins in the jejunum, helps regulate glucose homeostasis in the human body.

Methods: In Paper I, jejunal mucosa biopsies in patients undergoing RYGB surgery, and biopsies retrieved from the Roux limb 6-8 months after surgery were assessed with proteomics. The proteomics findings were further studied *in vivo* in mice and *in vitro* in murine primary jejunal enteroendocrine cells (EECs). In Paper II and III, the effect of two weeks of iso-caloric high-fat diet (HFD) and high-carbohydrate diet (HCD) were assessed in healthy, normal weight volunteers in a cross-over design. For Paper II, a mixed meal test (MMT) with sequential blood sampling was performed at end of each dietary period to examine the glucose homeostasis. Metabolomics was also used to explore the effect of each dietary period on metabolite profiles. For Paper III, jejunal mucosa biopsies were retrieved following each dietary period, and assessed with western blot and Ussing chambers. The findings were further studied *in vitro* in Caco-2 cells. In Paper IV, *in vitro* cultures of murine GLUTag cells and differentiated human jejunal enteroid monolayers were used to study the effect of the ketone body β-hydroxybutyrate (βHB) on glucose-induced GLP-1 secretion.

Result: It was shown that the ketogenesis rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) is drastically down-regulated in jejunum after RYGB. Furthermore, prolonged HFD in mice increased the jejunal expression of the same enzyme. In the diet study, MMT resulted in similar glucose and insulin profiles, while the secreted levels of GLP-1 and several metabolites, *i.e.* valine, leucine and creatine, previously been shown to be indicators of early insulin resistance were elevated. HFD decreased the expression of sodium-glucose linked transporter 1 (SGLT1) and the acetylation of histone 3 at lysine 9 in jejunum, while the expression of HMGCS2 was increased. *In vitro* studies in Caco-2 cells stipulate a sirtuin dependent regulation of SGLT1 expression, induced by jejunal ketogenesis. βHB had an inhibitory effect on glucose-induced GLP-1 secretion in murine primary jejunal EECs, GLUTag cells and differentiated human jejunal enteroid monolayers. Addition of βHB to GLUTag cells increased phosphorylation of kinase Akt as well as expression of kinase ERK1/2.

Conclusions: The results display an interesting role of intestinal ketogenesis. The rate-limiting enzyme of ketogenesis HMGCS2, and therefore intestinal ketogenesis, is induced by a prolonged fat-dominated diet, and is almost completely abolished following RYGB surgery. The results also display a capacity of the jejunal ketogenesis to influence glucose homeostasis both by inhibition of GLP-1 secretion from EECs and by regulation of jejunal glucose transporters.

Keywords: glucose homeostasis, ketogenesis, jejunum

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